UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/062,831	02/05/2002	Steven M. Ruben	PZ006G13AP1C1D1	1783

22195 7590 09/08/2004

HUMAN GENOME SCIENCES INC
INTELLECTUAL PROPERTY DEPT.
14200 SHADY GROVE ROAD
ROCKVILLE, MD 20850

EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 09/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/062,831	RUBEN ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-10,13,14,24-31,34 and 35* is/are allowed.

6)☒ Claim(s) *11,12,15-23,32,33 and 36-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent applications (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

The specification should be amended to indicate that U.S. Application No. 09/690454 has issued as U.S. Patent No. 6,531,447.

2. Applicant's IDS, filed 02/05/02, is acknowledged. Applicant's references AA and AB, which contain partial material from the specifications of pending U. S. Application Numbers 09/912293 and 09/912,292 respectively, have been initialed and considered, but they have been crossed out as they are not appropriate for an IDS.

3. Claims 1-75 are pending and under examination as they read on an antibody that specifically binds the polypeptide of SEQ ID NO: 59 or a cell that produces said antibody. Because there is ambiguity as to the sequence correspondence of the polypeptide endoded by cDNA clone HEMCM42 in ATCC Depsoit Number 209075 to that of SEQ ID NO: 59, claims 38-75 are examined under art to the extent of SEQ ID NO: 59 only.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112.
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 11, 12, 22, 23, 32, 33, 48, 49, 59, 60, 70 and 71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 11, 32, 48, and 70 have insufficient antecedent basis in the independent claims from which they depend (claims 1, 17, 38, and 54 respectively), because the independent claims recite an "antibody or fragment thereof" per se, whereas the depended claims recite an "antibody or fragment thereof which is labeled". It is suggested that claim 11, for example, be changed to "A labeled antibody or fragment thereof, wherein the antibody or fragment thereof of claim 3 is labeled." Claims that are dependent from claims reciting labeled antibodies (claims 12, 33, 49, and 71) also lack appropriate antecedent basis. It is suggested that claims 12, 33, 49, and 71 be changed to, for example, "The labeled antibody or fragment thereof of claim ... ".

B. Claims 22, 23, 59, and 60 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

Independent claims 17 and 54 recite an antibody that is produced by an animal immunized with a protein. This immunization process will generate a polyclonal antibody response in the animal, and therefore the antibody product obtained by said process will be polyclonal in nature. Dependent claims 22 and 59 recite that the antibody is monoclonal, while dependent claims 23 and 60 recite that the antibody can be chimeric, humanized, single chain, or a Fab fragment. The antibody forms recited in the dependent claims can be made in a laboratory setting from starting materials obtained from the immunized animal, but without the incorporation of additional method steps germane to making the recited antibody types, it is unclear how this will be accomplished.

C. Applicant is reminded that any amendment to the claims to obviate a rejection must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 17-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody that binds a protein **consisting of** SEQ ID NO: 59, residues 30-113 of SEQ ID NO: 59, 30 contiguous residues of SEQ ID NO: 59, or 50 contiguous residues of SEQ ID NO: 59, does not reasonably provide enablement for an antibody that binds a protein that **comprises** residues 1-113 of SEQ ID NO: 59, residues 30-113 of SEQ ID NO: 59, 30 contiguous residues of SEQ ID NO: 59, or 50 contiguous residues of SEQ ID NO: 59. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification discloses, on pages 24 and 25 in the section headed Features of Protein Encoded by Gene No: 13, various uses for an antibody that has specificity for SEQ ID NO: 59. The specification discloses some preferred epitopes on page 25, line 4, but there appears to be insufficient evidence that these epitopes were ever used to generate antibodies that could be used in the disclosed utilities. Applicant's claimed invention is not limited to these epitopes, but instead has a broad scope that encompasses any number of undisclosed amino acids that may be added to either end of residues 1-113 or 30-113 of SEQ ID NO: 59, or to a polypeptide that has 30 or 50 contiguous amino acids of SEQ ID NO: 59. Guidance in selecting appropriate 30 or 50 contiguous amino acids for use making antibodies that retain the disclosed utilities appears to be lacking.

Antibodies are produced by immunizing an animal with an antigen, with the specificity of the resulting antibodies being directed to linear epitopes or conformational domains that are particularly immunogenic (Janeway et al., Immunobiology, 1997, see particularly the second full paragraph on page 2:2, and the last paragraph of page 3:9). As such, an antibody isolated from an animal immunized with a protein that comprises residues 1-113 of SEQ ID NO: 59, residues 30-113 of SEQ ID NO: 59, 30 contiguous residues of SEQ ID NO: 59, or 50 contiguous residues of SEQ ID NO: 59, may bind to the region of the protein that corresponds to the undisclosed sequence that is incorporated by the comprising language and not to the part that consists of some portion of SEQ ID NO: 59, or it may potentially bind a conformational epitope formed by the interplay of undisclosed and SEQ ID NO: 59 residues. Additionally, the antibody may bind to a region of SEQ ID NO: 59 that is not compatible with the disclosed utilities of screening assays, treatments for vascular disorders and other methods disclosed on pages 24 and 25 of the instant specification that demonstrated the utility of the polypeptide consisting of SEQ ID NO: 59 as established in the prosecution of U.S. Patent No. 6,531,447, to which this application claims priority.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. Due to the unpredictability in the specificity and utility of the antibodies generated by immunizations with peptides comprising residues 1-113 of SEQ ID NO: 59, residues 30-113 of SEQ ID NO: 59, 30 contiguous residues of SEQ ID NO: 59, or 50 contiguous residues of SEQ ID NO: 59, and the limited guidance concerning which residues of SEQ ID NO: 59 are important for utility, undue experimentation would

be required by one of skill in the art to use such antibodies in the disclosed applications of vascular disorder treatments and screening assays.

8. Claims 38-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody that binds a protein encoded by cDNA HEMCM42 that consists of SEQ ID NO: 13 and that encodes the polypeptide consisting of SEQ ID NO: 59, does not reasonably provide enablement for an antibody that binds any polypeptide encoded by the cDNA HEMCM42. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 38-75 recite a "polypeptide encoded by the cDNA HEMCM42 contained in ATCC Deposit Number 209075" but it is not clear if cDNA HEMCM42 is limited to consisting of SEQ ID NO: 13 (the disclosed polynucleotide sequence that encodes SEQ ID NO: 59). Therefore, the claims have been interpreted in the broadest reasonable manner in light of the specification to include **any** protein encoded by the cDNA HEMCM42. Note that this means that the polynucleotide sequence of cDNA HEMCM42 may or may not be identical to SEQ ID NO: 13, and the polypeptide encoded by said polynucleotide sequence may or not be identical to SEQ ID NO: 59. If the sequence of HEMCM42 is identical to that of SEQ ID NO: 13, this should be indicated in the claims. Additionally, claims 54-60 also include comprising language that allow the addition of undisclosed amino acid to either end of a portion of the polypeptide encoded by cDNA HEMCM42, wherein said undisclosed amino acids are not encoded by cDNA HEMCM42.

This biological material of uncertain sequence, cDNA HEMCM42, has been deposited as ATCC Deposit Number 209075, and it is apparent that this material is essential to the claimed invention. The disclosure indicates that ATCC Deposit Number 209075 contains many different plasmids, all marked with the same antibiotic resistance gene (Amp^r). As such, transformation of the material contained in ATCC Deposit Number 209075 into bacteria will allow for the selection of bacteria that contain plasmid(s) marked with the antibiotic resistance gene, but will not allow for the direct selection of HEMCM42 per se. Therefore, there is no way to ensure that cDNA HEMCM42 will be maintained in culture, since this plasmid could be lost even though the bacteria maintain their antibiotic resistance.

Standard library screening techniques disclosed in the specification (page 105, lines 23-36) may not be a reliable method to isolate HEMCM42, since a probe would need to be generated based on SEQ ID NO: 13, a sequence that may be different from the claimed invention. Additionally, a clone isolated through such a screen may contain additional plasmids that encode different polypeptides yet have the same antibiotic resistance marker and consequentially, the cell may not maintain HEMCM42 after repeated passages in culture. Thus the cells isolated by the screen are not appreciably different from the starting cellular material before the screening process.

The alternative disclosed method, using PCR to isolate HEMCM42 (page 106 lines 1-13), would also be problematic since PCR can introduce mutations as part of the amplification process. Since the sequence of cDNA HEMCM42 may be different from that of SEQ ID NO: 13, and thus it may encode a polypeptide different than that of SEQ

ID NO: 59, it would not be possible to know if the sequence obtained via PCR was genuine or an artifact of amplification.

In light of the unpredictability of factors discussed in obtaining cDNA HEMCM42 above, and the limited guidance presented in the specification concerning the regions of the molecule important for its function as well as contemplated additions to the polypeptide sequence encoded by cDNA HEMCM42, it appears that undue experimentation would be required by a person of skill in the art to practice the full breadth of the invention as claimed.

Additionally, it is noted that the specification indicates on page 3, lines 18-20, that cDNA clone HEMCM42, ATCC Deposit Number 209075, was deposited under the terms of the Budapest treaty but assurances that this material will be irrevocably and without restriction or condition released to the public upon the issuance of a patent appear to be absent.

If the deposit has been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the cDNA clone HEMCM42 has been deposited under the Budapest Treaty and that the cDNA clone HEMCM42 will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or for the

enforceable life of the patent, whichever is longer. See 37 CFR 1.806 and MPEP 2410-2410.01. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

If the deposit was made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the vector described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

9. Claims 15-23, 36, 37, 52-60, 74, and 75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody obtained from an immunized animal, or an isolated cell or a hybridoma that produces an antibody, does not reasonably provide enablement for an immunized animal, an isolated cell or a hybridoma that makes a fragment of an antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Antibodies are secreted by plasma cells (in the immunized animal) or hybridomas as intact antibody molecules that contain two heavy and two light chains liked by disulfide bonds (Janeway et al., pages 1:6, 2:17-2:18, and 3:2 to 3:5 in particular). The antibody molecule must then be harvested and proteolytically cleaved with papain or pepsin to yield fragments such as Fab and $F(ab')_2$ respectively (Janeway et al., particularly pages 3:3-3:4). As such, fragments cannot be generated directly by the immunized animal, isolated cell or hybridoma. The specification on page 80, lines 11-19, defines antibody as including intact molecules as well as fragments such as Fab and $F(ab')_2$, and chimeric, single chain, and humanized antibodies. Each of these molecules has a unique structure that imparts it with a specialized function that can be exploited in various methods (Janeway et al., section 3-3, pages 3:3 to 3:5 in particular), but they all require the hand of man, be it through chemical or recombinant technologies, to make such fragments after isolating the starting material (whole antibody) from the animal, cell, or hybridoma. Since these materials cannot be made as disclosed by the specification, they cannot be used in any of the methods disclosed in Features of Protein Encoded by Gene No: 13, and Uses of the Polypeptides (pages 24-25 and 87-88 of the instant specification, respectively).

10. Claims 17-23 and 54-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification provides adequate written description for how to make an antibody that binds a protein **consisting of** amino acids 1-113 of SEQ ID NO: 59, amino acids 30-113 of SEQ ID NO: 59, 30 contiguous residues of SEQ ID NO: 59, or 50 contiguous residues of SEQ ID NO: 59, but it does not provide sufficient written description for how to make an antibody that binds a protein that **comprises** amino acids 1-113 or 30-113 of SEQ ID NO: 59, or an antibody that binds a protein **comprising** 30 or 50 contiguous amino acids of SEQ ID NO: 59 as recited in claims 17-23.

Similarly, the specification provides adequate written description for making an antibody that binds a protein **consisting of** the full length, mature, or a series of contiguous amino acid either 30 or 50 residues in length encoded by HEMCM42 cDNA, but there is insufficient written description to encompass making an antibody that binds to a protein **comprising** the full length, mature, or a series of contiguous amino acid either 30 or 50 residues in length encoded by HEMCM42 cDNA in ATCC Deposit Number 209075, claims 54-60, because the relevant identifying characteristics such as structure or other physical and/or chemical characteristics of HEMCM42 cDNA as well as the undisclosed sequences encompassed by the comprising language are not set forth in the specification as filed. Further, there is no written description of which 30 or 50 contiguous amino acids of either SEQ ID NO: 59 or the polypeptide encoded by

HEMCM42 cDNA are important for generating antibodies that are useful in performing the disclosed methods.

The term comprising is open, thus allowing any number of undisclosed amino acids to be added to either end of residues 1-113 or 30-113 of SEQ ID NO: 59, or to a polypeptide that has 30 or 50 contiguous amino acids of SEQ ID NO: 59, or to either end of a protein comprising the full length, mature, or a series of contiguous amino acids either 30 or 50 residues in length encoded by HEMCM42 cDNA. Such language encompasses heterologous fusion proteins that contain domains having biological activities that are separate from that of SEQ ID NO: 59 (TWEAKR/Fn14/HEMCM42). Antibodies that specifically bind such proteins may specifically interact with portions of the molecule that do not consist of SEQ ID NO: 59, yet Applicant has only disclosed SEQ ID NO: 59. Additionally, applicant has not disclosed which portions of SEQ ID NO: 59 when bound by an antibody have a disclosed utility. Therefore, it is not possible for the skilled artisan to envision all the possible antibodies encompassed by the scope of the instant claims due to the number of proteins which comprise SEQ ID NO: 59 and even greater number of epitopes that are found on proteins that comprise SEQ ID NO: 59.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co.

Ltd., 18 USPQ2d 1016.

Conception of the claimed invention cannot occur until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the invention. However, one cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

In the absence of such identifying structural characteristics that provide for utility and are shared by all sequences present in the genus of sequences that may be added to a protein that comprises resides 1-113 of SEQ ID NO: 59, residues 30-113 of SEQ ID NO: 59, 30 contiguous residues of SEQ ID NO: 59, 50 contiguous residues of SEQ ID NO: 59, or a protein that comprises the full length, mature, or a series of contiguous amino acid either 30 or 50 residues in length encoded by HEMCM42 cDNA, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe said genus, and as such one can not envision the structure of the genus of antibodies that would bind to said proteins comprising SEQ ID NO: 59. Thus, Applicant was not in possession of the claimed genus of the instant invention. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

11. Claims 1-10, 13, 14, 24-31, 34, and 35 are allowable because sequences consisting of SEQ ID NO: 59 appear to be free of the prior art.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
Tech Center 1600
9/1/04

Michael Szperka, Ph.D.
Patent Examiner
Technology Center 1600
August 24, 2004